## REMARKS

### The January 17, 2006 Interview

Applicants thank Examiner Chen for her willingness to have an interview with applicants' attorney and representatives of applicants' licensee, Acambis, so soon after taking over responsibility for this application and its continued examination.

At the interview, the pending enablement rejection was discussed. Applicants' attorney and the technical representatives of applicants' licensee discussed the mice data reported in the application and the subsequently published mice, ferret, swine, rabbit and monkey data of others. They also addressed some of the on-going work that licensee is conducting in the context of the claimed invention.

At the interview, Examiner Chen and applicants' attorney also discussed possible claim amendments to direct the claims to an "immunogenic composition" rather than to a "vaccine." Applicants have, instead, amended the claims into method of use format. This format captures the intent of the claim amendment discussed at the interview without exposing the claim to potential art that has reported a fusion of an M2e region and a presenting carrier. *See, e.g.*, Lamb et al., *Cell*, 40:627-633 (1985) at p. 627. *See* Information Disclosure Statement, October 15, 2003.

### The Claim Amendments

Claims 26-32, 34, 36-41, 46, 52-57 and 58 are pending.

Applicants have amended all of the previously pending claims and added claim 58. In sum, applicants have amended the claims to recite a method for reducing the severity or lethal

potential of an influenza infection by administering to the person or animal at risk of such infection, in an amount effective for that reduction, a composition comprising the recited fusion product. This amendment finds support throughout the specification. *See, e.g.*, p. 42, lines 4-24; p. 44, line 35; page 45, line 17; p. 53, line 34; page 54, line 3; and p. 55, lines 25-36. *See* also Figures 8 A-D.

The above amendments present the claims in better form for consideration on appeal and address the pending enablement rejection. 37 C.F.R. § 1.116. Applicants request that they be entered.

**Rejection Under 35 U.S.C. § 112, first paragraph**

All of the pending claims stand rejected for lack of enablement. Applicants traverse.

As discussed at the interview, the application, as filed, presents actual Examples demonstrating that mice -- a recognized model for human influenza infection and treatment -- survived lethal challenge with human influenza A virus after administration of compositions according to this invention. Indeed, the Examples demonstrate that, using two different M2e sequences, three different doses, two modes of administration, and challenge with two different viral strains, 8 to 12 out of the 12 treated mice survived the challenge as compared to 2 out of 11 of the controls. *See, e.g.*, p. 42, lines 4-24; and p. 44, line 35 – p. 45, line 17.

A number of subsequent reports from the scientific literature confirm the advantageous and useful effect of the methods of this invention in lessening the severity of human influenza infection or in reducing the possibility of death caused by such infections. In these

reports, mice and other animal models were used. And, in these reports other compositions of this invention, *i.e.*, non-genetic fusions, other heterologous presenting carriers, and other challenge viruses were successfully used.

For example, Fan et al., *Vaccine*, 22:2993-3003 (2004) ("Fan") reports work at the Merck Research Laboratories. In that work, M2e fusion compositions according to this invention were tested in mice, ferrets and monkeys. The compositions, assessed in Fan, consisted of human influenza M2 extracellular domains fused by chemical conjugation at the N- or C-terminus to either a keyhole limpet hemocyanin (KLH) carrier or a *N. meningitides* outer membrane protein complex (OMPC) carrier (*see* Table 1, p. 2996).

In the same mice challenge model used by applicants, Fan and his fellow Merck researchers reported that 90-100% of the mice treated with the M2-KLH conjugate survived challenge with a 90% lethal dose of two different human influenza viruses, as compared with a survival of only 10-20% of the controls. *See* p. 2996, right hand column. Fan also reported that the morbidity of the infection in the treated mice was less than in the control, *i.e.*, the treated mice had reduced weight loss as compared to the control mice. *Id.* Finally, Fan reported that the treated mice exhibited overall lower viral shedding in both nasal and lung than did the control mice. *Id.* Fan's conclusion from its mouse data was clear: "The results therefore establish that the M2 peptide conjugate vaccines can provide protections against virus with different HA subtypes." *Id.*

In ferrets -- another recognized animal model for human influenza infection and treatment (a model where death is not an endpoint, rather viral shedding and morbidity due to the

infection are assessed) -- Fan reported that ferrets, treated with four different forms of M2 conjugates (*see* Table 1), developed significant M2-specific antibodies and exhibited reduced lung viral shedding as compared to controls. *See* pp. 2997-2999.

Fan also reported immunizing monkeys with an M2-OMPC conjugate and transferring the antibodies raised in the monkeys to mice. Mice treated with high titer sera from the immunized monkeys survived lethal influenza challenge. Control mice did not. *See* pp. 2999-3000.

Fan concluded that its data supported the concept that an M2 peptide-carrier fusion could be used as "an adjunct to the current vaccine products for elicitation of broadly-reactive and clinically protective anti-influenza virus A antibodies. Such a vaccine would not have to be updated annually and could serve as a possible pediatric vaccine that could provide early protection against influenza virus-mediated diseases. *See* p. 3002.

Other research groups have reported similar results. For example, Liu et al., *Vaccine*, 23:366-371 (2004) ("Liu") (a research group from the Tsinghua University in Beijing) (copy enclosed) reported that fusion proteins comprising several copies of an M2e epitope fused to glutathione-S-transferase proteins, when used to immunize mice (again the model that applicants have used), protected them from a lethal human influenza virus challenge. Indeed, the GST-$(M2e)_{16}$ conjugate provided complete protection. *See* p. 369. And, the GST-$(M2e)_4$ provided 50% protection. *Id.* Further, the mice treated with the higher density M2e fusion proteins showed reduced morbidity, as evidenced by less weight loss on influenza challenge. *Id.*

Mozdzanowska et al., *Vaccine*, 21:2616-62 (2003) ("Mozdzanowska") (a research group from the Wistar Institute) reported similar results. Multivalent M2e-MAP and M2e-Man-MAP fusion constructs carrying four copies of M2e successfully immunized mice. After challenge ($10^3$ 50% mouse infectious doses), the mice showed reduced virus growth in all parts of the respiratory tract. *See* p. 2624.

With these results in hand, Mozdzanowska summarized the state of the art in 2003: "Several distinct M2 vaccine constructs have been developed by different groups ([1-4]; present study) and found to induce significant resistance to influenza type A virus replication in mice." *See* p. 2625.

Against these diverse demonstrations and actual evidence that the claimed fused compositions lessen the severity of influenza infection and protect mice -- a standard animal model for influenza -- from lethal challenge, the former Examiner pointed to several documents -- Heinen, Jegerlehner, Zharikova and Chen. None of them changes the fact that the application enables the claimed methods.

The lynchpin of the former Examiner's arguments is Heinen, *J. Gen. Virology*, 83:1851-59 (2002) ("Heinen"). Heinen reports the swine-based testing of an M2e-HBc fusion that the inventors of this application had provided to them. *See* p. 1852. Heinen concluded that the composition did not protect the swine from challenge and may have exacerbated the disease. *See* Abstract.

Heinen's experiments were flawed and do not support any conclusions about the effectiveness of applicants' claimed fused compositions or methods. First and foremost, the

amino acid sequence of the M2e portion of the swine virus used in Heinen's challenge differed from the M2e fusion partner used to immunize the swine by 26% (six differences out of 23 amino acids). *See* p. 1852. This difference is far too large to draw any conclusion about the effectiveness of the M2e construct against infection by human influenza viruses which over many years have displayed remarkable sequence conservation in the M2e region. *See, e.g.*, Table I of the application , p. 4. Indeed, an antigenic drift in a human influenza virus of only 2-3% reduces the ability of the yearly vaccine to be effective in subsequent years. Heinen, itself, points to this sequence divergence as one reason why its results are different from those reported in this application. *See* p. 1857.

Second, perhaps not recognizing the antibody-dependent cellular cytotoxicity ("ADCC") mechanisms that is believed to characterize the M2e-based compositions of this invention, Heinen used a very high titer viral challenge -- $10^8$ $TCID_{50}$ (median tissue culture infective dose). *See* p. 1853. This challenge likely overwhelmed the Swine's immune response to the M2e fusion. Indeed, Heinen points to the titer of its challenge as another reason why its results were inconsistent with those reported by other groups using the fused compositions of this invention. *See* p. 1858. As a consequence of at least these two experimental flaws, Heinen in no way provides evidence that applicants' composition and method are not enabled.

The former Examiner next points to Jegerlehner et al., *J. Immunology,* 172:5598-5605 (2004) ("Jegerlehner"). Again, her reliance is misplaced.

Jegerlehner investigated the possible mechanisms of actions of M2e-HBc fusion proteins against the influenza virus. *See* p. 5599. Jegerlehner concluded that, while the fusion

induced protective antibodies, they were not neutralizing antibodies. *Id.* Jegerlehner then proposed that the mechanism of action was an antibody-dependent cellular cytotoxicity mechanism in which NK cells played a role. *See* pp. 5599, 5605.

Consistent with this mechanism, Jegerlehner reported that protection was "weak overall and failed to prevent weight loss in vaccinated animals" and that "mice succumbed to *high dose* infection" (emphasis added). More importantly, however, Jegerlehner reported: "M2e-HBc-immunized mice showed 100% protection against infection with a lethal dose of influenza A virus PR8" and that "mice immunized with M2-HBc are protected. They show signs of disease, which is visible as weight loss, before recovery from illness." *See* pp. 5600 and 5604. Jegerlehner also concluded that the "protection induced by the M2 vaccine is exclusively mediated by [antibodies], which allows the assumption that the vaccine would induce long term protection." *See* p. 5603.

Thus, contrary to the former Examiner's contentions, Jegerlehner provides further evidence of the effectiveness of the M2e fusions of this invention. Indeed, while Jegerlehner suggests that the fusions would not be "suitable" for use during an epidemic, where "full protection with no sign of disease is the goal" (emphasis added), it would be useful "to prevent or at least reduce mortality during a pandemic." *See* p. 5604-5605. In fact, Jegerlehner argues that the M2e-HBc fusion would have been effective against the 1918 pandemic which killed 20-40 million people worldwide. *See* p. 5605.

That the occurrence of the next pandemic may be speculative, as the former Examiner contends, does not make applicants' claimed compositions not enabled. There have been three pandemics since 1918. There will likely be another. The claimed M2e compositions

will reduce mortality in such pandemic. They are useful. Furthermore, the claimed compositions are useful, *inter alia*, as an adjunct to the yearly NA/HA vaccine. *See* Zharikova, *infra*; *Fan*, *supra*, and application, p. 9, lines 12-15. Indeed, in several years the match between the predicted and circulating virus was poor. *E.g.*, 1947, 1997, and 2003. In these years, this yearly HA/NA vaccine was less effective than hoped. *See, e.g., Kilbourne et al.*, PNAS, 99:10748-52 (2002) (copy enclosed). The composition of this invention would have improved the effectiveness of the vaccines. The M2e region is highly conserved year to year.

The former Examiner next points to Zharikova, *J. Virology*, 79:6644-54 (2005) ("Zharikova"). She contends that the escape mutants observed in Zharikova suggest that the claimed M2e fusion is not enabled. The former Examiner is mistaken.

Zharikova reports that, while "M2e-specific antibodies cannot prevent virus from initiating an infection or resolve an established infection, . . . they can diminish the yield of infectious virus and thus inhibit progression of the infection." *See* p. 6647. Zharikova also reports that the results of its study "confirm the protective activity of M2e-specific antibodies *in vivo.*" *See* p. 6653. Finally, Zharikova concludes that "M2e could be used as an adjunct to current vaccines and provide a protective safety net in the case of a major antigenic disparity between vaccine and circulating epidemic strains. *See* p. 6653. In fact, contrary to the former Examiner's contentions, Zharikova specifically argues that the fact that escape mutants arose in its passive immunity experiments did not "preclude use of M2e as a generic vaccine against influenza type A viruses as long as the structural variation remains small and all major variants can be incorporated into a "polyvalent - M2e vaccine" which Zharikova acknowledges can easily be done. *See*

pp. 6645 and 6653. Thus, again the former Examiner's reliance on Zharikova to attack the enablement of the pending claims is not supported by the conclusions of Zharikova themselves.

Finally, the former Examiner points to Chen et al., *Vaccine*, 19:1446-555 (2001) ("Chen") as supposed evidence that the claimed NB-based compositions and methods are not useful against influenza B virus infections. Again, the former Examiner is mistaken. Chen did not test a composition of this invention. Its NB antigen was not fused to a carrier. *See* p. 1447. Chen, thus, provides no evidence that applicants' invention is not enabled.

## CONCLUSION

Applicants respectfully request that Examiner Chen consider the above arguments and diverse scientific reports of the effectiveness, mechanism of actions and usefulness of the claimed M2e-based methods and allow the pending claims. The Examiner is invited to telephone the undersigned to discuss any issues remaining in this application.

Respectfully submitted,

James F. Haley, Jr. (Reg. No. 27,794)
Z. Ying Li (Reg. No. 42,800)
Attorneys for Applicants
R. Minako Pazdera (Reg. No. 46,984)
Agent for Applicants
c/o FISH & NEAVE IP GROUP
ROPES & GRAY LLP
Customer No. 1473
1251 Avenue of the Americas
New York, New York 10020
Tel.: (212) 596-9000
Fax.: (212) 596-9090